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Influenza Vaccine Effectiveness Against Pediatric Deaths: 2010–2014

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Abstract

BACKGROUND AND OBJECTIVE—Surveillance for laboratory-confirmed influenza-associated pediatric deaths since 2004 has shown that most deaths occur in unvaccinated children. We assessed whether influenza vaccination reduced the risk of influenza-associated death in children and adolescents.

METHODS—We conducted a case-cohort analysis comparing vaccination uptake among laboratory-confirmed influenza-associated pediatric deaths with estimated vaccination coverage among pediatric cohorts in the United States. Case vaccination and high-risk status were determined by case investigation. Influenza vaccination coverage estimates were obtained from national survey data or a national insurance claims database. We estimated odds ratios (OR) from logistic regression comparing odds of vaccination among cases with odds of vaccination in comparison cohorts. We used Bayesian methods to compute 95% credible intervals for vaccine effectiveness (VE), calculated as (1 – OR) × 100.

RESULTS—From August 2010 through July 2014, 358 laboratory-confirmed influenza-associated pediatric deaths were reported among children aged 6 months through 17 years. Vaccination status was determined for 291 deaths; 75 (26%) received vaccine before illness onset. Average vaccination coverage in survey cohorts was 48%. Overall VE against death was 65% (95% credible interval: 54–73). Among 153 deaths in children with underlying high-risk medical

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Dr Flannery conceptualized and designed the study, carried out analyses, drafted the initial manuscript, and approved the final manuscript as submitted.
Ms Blanton, O'Halloran and Drs Santibanez, and Lu carried out the initial analyses, contributed to and reviewed the manuscript, and approved the final manuscript as submitted.
Drs Reynolds, Chen, Foppa and Gargiullo conceptualized and carried out statistical analyses, contributed to and revised the manuscript, and approved the final manuscript as submitted.
Drs Bresee, Singleton and Fry contributed to study design, critically reviewed the manuscript, and approved the final manuscript as submitted.

conditions, 47 (31%) were vaccinated. VE among children with high-risk conditions was 51% (95% credible interval: 31-67), versus 65% (95% credible interval: 47-78) among children without high-risk conditions.

CONCLUSIONS—Influenza vaccination was associated with reduced risk of laboratory-confirmed influenza-associated pediatric death. Increasing influenza vaccination could prevent influenza-associated deaths among children and adolescents.

INTRODUCTION

In the United States, annual influenza vaccination of children is recommended to reduce adverse health impacts of influenza and prevent severe complications.[1] While uncommon, influenza-associated deaths among children occur annually with varying incidence depending upon the severity of the influenza season.[2, 3] From 1976 to 2007, influenza was estimated to account for more than 100 deaths annually among children and adolescents.[4, 5] Since 2004, when influenza-associated deaths among children aged <18 years became nationally notifiable,[6] reported numbers of deaths have ranged from 37 in the 2011-2012 season to 282 during the 2009 pandemic.[2] Surveillance for pediatric deaths has contributed to identification of groups at high risk of influenza-related mortality such as children with neurologic conditions,[7] as well as documenting fatal illness among children with and without underlying high-risk medical conditions.[3] Previous reports have indicated low rates of influenza vaccination among pediatric deaths despite high prevalence of underlying medical conditions that increase risk for influenza complications.[3, 8] In this analysis, we used a case-cohort approach comparing influenza vaccination rates among influenza-associated pediatric deaths with vaccination coverage estimates for cohorts of U.S. children to estimate effectiveness of influenza vaccination against laboratory-confirmed influenza associated death.

METHODS

Influenza-Associated Pediatric Deaths

To estimate influenza vaccine effectiveness against death, we used a case-cohort design (or screening method).[9, 10] Cases were deaths in U.S. residents aged <18 years with laboratory-confirmed influenza virus infection that were reported to the Influenza-Associated Pediatric Mortality Surveillance System.[3] Data obtained from standardized case report forms included demographic characteristics, state of residence, results of laboratory testing, underlying high-risk medical conditions and influenza vaccination status. Confirmation of influenza virus infection included clinical diagnostic testing during illness or post-mortem examination using antigen detection, viral culture or nucleic acid amplification. We included children at least 6 months old on November 1 of the influenza season during which death occurred who were eligible to receive at least one dose of seasonal influenza vaccine and had complete medical history; 10 deaths among children who turned 6 months old after November 1 were excluded. For cases without illness onset date, we estimated onset as four days before death based on the mean duration of illness among cases with known onset date. We excluded seven children who received their first dose of current season vaccine <14 days before illness onset because vaccine-induced protection may be incomplete.[11]

Health department personnel determined vaccination status based upon review of available information from the child's medical records, health care provider, state or county immunization information systems, parental report or coroner's report. Children were considered vaccinated (either fully or partially) if records indicated receipt of 1 or more doses of current season influenza vaccine at least 14 days before onset of illness. Partial vaccination was defined as receipt of one dose when health department personnel determined that two doses were indicated. Vaccination status was listed as unknown if surveillance personnel could not determine from available records if the child had received influenza vaccine. If immunization records indicated vaccination for prior seasons but no current season vaccination, children were assumed to be unvaccinated. A sensitivity analysis explored effects of assuming that children with unknown vaccination status were unvaccinated. Presence of underlying medical conditions was recorded on case report forms according to high-risk conditions for influenza-related complications identified by the Advisory Committee on Immunization Practices:[12] asthma, chronic lung disease, neurologic/neurodevelopmental disorders, heart disease (including congenital heart disease), blood disorders, endocrine disorders, metabolic disorders, kidney disorders, liver disorders, immunosuppression and pregnancy. For consistency with vaccination coverage estimates, age groups were defined based on child's age on November 1 for influenza season of fatal illness.

Influenza Vaccination Coverage in Cohorts

We used three sources of influenza vaccination coverage among comparison cohorts of U.S. children and adolescents: National Immunization Survey-Flu (NIS-Flu),[13] National Health Interview Survey (NHIS)[14] and the MarketScan Commercial Claims and Encounters database (Truven Health Analytics, Ann Arbor, Michigan). NIS-Flu is a national telephone survey of households with children aged 6 months through 17 years that produces national and state-level estimates (and for some cities, including Chicago and New York City) of influenza vaccine coverage for children. NHIS is an in-person household survey that provides nationally representative estimates of influenza vaccination for children aged 6 months through 17 years with and without specified high-risk medical conditions (cystic fibrosis, sickle cell anemia, diabetes, congenital heart disease or other heart condition, cerebral palsy, muscular dystrophy, or seizures; or an asthma episode in the past 12 months.)[15] In NIS-Flu and NHIS, seasonal influenza vaccination coverage is estimated from parental report of child's receipt of ≥1 dose of seasonal influenza vaccine. Data from NIS-Flu and NHIS are weighted by age, sex, race/ethnicity and geographic area to represent the U.S. population. Monthly coverage estimates and standard errors for vaccination received during July or August (depending upon survey and season) through May were calculated by Kaplan-Meier survival analysis of data from interviews conducted from August, September or October through June.[16] Age group was based upon the child's age on November 1 of each influenza season.

In the MarketScan Commercial Claims and Encounters database, coverage estimates were based on commercial insurance claims for influenza vaccination; children with no vaccination claim were assumed unvaccinated. We analyzed data from July 2010 through June 2014 among children continuously enrolled in a health plan from January preceding

each influenza season. We determined underlying high-risk medical conditions based on International Classification of Disease 9th revision codes associated with hospitalizations and outpatient visits during a 12-month period.[17] We calculated cumulative vaccination coverage from August through May each season among children aged <18 years with and without underlying high-risk medical conditions. Age categories were based on child's age at vaccination or at the beginning of each calendar year; children in the youngest age category (0-4 years) were at least 10 months old on November 1. For MarketScan comparison cohorts, state-level coverage estimates were used for children without high-risk conditions while national coverage estimates were used for children in high-risk groups due to smaller sample sizes.

Analysis

The case-cohort method[9, 10] produces an odds ratio (OR), which estimates the relative risk for influenza-associated death among vaccinated versus unvaccinated children. Influenza vaccine effectiveness (VE) was estimated as (1 – OR). ORs were obtained from logistic regression models where vaccination status of the case was the dependent variable and the log odds of vaccination (proportion vaccinated/1 – proportion vaccinated) in the comparison cohort from NIS-Flu, NHIS, or MarketScan data was entered as an offset. With this offset in the model, the intercept provides an estimate of the log(OR). Cases and corresponding coverage estimates were stratified by influenza season, age, and state of residence (for NIS-Flu and MarketScan) or high risk condition (for NHIS and MarketScan) for the month ending at least two weeks before case illness onset. For average coverage estimates by age group, season or influenza virus type, we derived confidence limits by averaging the variance of independent, normally-distributed coverage estimates. To incorporate uncertainty in coverage estimates from survey data, 10,000 estimates were sampled from normally distributed vaccination coverage estimates for NIS-Flu and NHIS comparison cohorts to calculate 95% credible intervals for VE estimates. Because MarketScan estimates were derived from all observations without sampling, confidence limits for VE estimates using MarketScan data were estimated from logistic regression assuming fixed coverage estimates. We assumed that cases did not contribute uncertainty to VE estimates. Sensitivity analyses were conducted assuming 1) cases with unknown vaccination status were unvaccinated and 2) coverage estimates based on parental report over-estimated coverage by 10% or 20%.[18, 19] χ^2 tests were used to evaluate proportions and two-sided P values < .05 were considered significant. Analyses were conducted in SAS, version 9.4 (SAS Institute, Cary, NC) and R (version 3.1.1; R Core Team, Vienna, Austria).

RESULTS

This analysis included 358 influenza-associated pediatric deaths that occurred during four influenza seasons from July 1, 2010 through June 30, 2014 among children aged 6 months through 17 years. Deaths were reported from 43 states, New York City, Chicago and Washington, D.C. Vaccination status was unknown for 67 (19%) children who died. Of 291 deaths in children with known vaccination status, 75 (26%) children had received seasonal influenza vaccination ≥14 days before illness onset and were considered vaccinated. Vaccine type was recorded for 62 cases: 12 (19%) received live-attenuated influenza vaccine and 50

(81%) received inactivated influenza vaccines. Vaccinated proportions were similar for males and females, and did not differ significantly by age category (Table 1). Black, non-Hispanic children had significantly lower vaccination rates compared with White, non-Hispanic children ($P < .05$). Among 31 deaths in vaccinated children aged 6 months through 4 years, 16 (52%) were partially vaccinated.

A total of 153 (53%) of 291 pediatric deaths with known vaccination status occurred among children with one or more ACIP underlying high-risk medical conditions. The prevalence of high risk conditions among pediatric deaths increased from 41% among those aged 6 months – 4 years to 57% and 62% among 5-12 and 13-17 year olds, respectively. While the proportion of children vaccinated increased from 20% among those without high-risk conditions to 31% among those with ≥1 high-risk condition and 37% among those with ≥2 high-risk conditions, fewer than 50% of children in all individual high-risk categories were vaccinated (Table 1).

Average influenza vaccination coverage among comparison cohorts in the month preceding case illness onset was higher than vaccinated proportions among pediatric deaths for most months (Figure). Among deaths in children with known vaccination status, children who died had lower vaccination uptake for all age categories, seasons, and infecting influenza virus types than the NIS-Flu cohort (Table 2). Overall, average vaccination coverage was 48% among NIS-Flu comparison cohorts. Estimated VE against pediatric death was 65% (95% credible interval [CI]: 54-74). Estimated VE ranged from 40% among 13-17 year olds to 76% among 5-12 year olds. By season, VE ranged from 54% in 2010-2011 to 80% (with overlapping confidence intervals) in the relatively mild 2011-2012 season with the lowest number of pediatric deaths. By virus type, VE point estimates were similar against death associated with influenza A virus (66%) and influenza B virus (62%).

Vaccination uptake among pediatric deaths was also lower than average coverage in the NHIS comparison cohorts with or without high-risk conditions (Table 3). Estimated VE was 51% (95% CI: 31-67) among children with high-risk medical conditions and 65% (95% CI: 47-78) among those without high-risk conditions, similar to VE estimated using NIS-Flu. VE point estimates were lower among children with high-risk conditions compared to those without high-risk conditions in most analyses, but credible intervals widely overlapped. Among children with high-risk conditions, VE estimates were statistically significant (95% credible intervals not overlapping zero) only for children aged 5-12 years. Estimated VE was statistically significant for three of four seasons among both children with and without high-risk conditions, for influenza A virus infections among both groups of children and for influenza B virus infections among children without high-risk conditions.

Table 4 compares the prevalence of high-risk conditions and uptake of influenza vaccination among influenza-associated pediatric deaths and children in the MarketScan database (including an average of more than six million individuals aged <18 years during the four influenza seasons). Vaccination coverage in MarketScan among children aged <18 years by high risk group ranged from 27% among those with no high-risk condition to 45% among children with two or more high-risk conditions (Table 4). Prevalence of high-risk conditions

was higher among pediatric deaths compared to the MarketScan cohort, and vaccination rates were lower among pediatric deaths for most high-risk groups.

In sensitivity analysis treating deaths with unknown vaccination status as unvaccinated, overall VE increased to 74% for the NIS-Flu cohort, 73% for the NHIS cohort without high-risk conditions and 50% for the MarketScan cohort without high-risk conditions (Table 5). Alternatively, assuming 10% over-estimation of vaccination by parental report in the survey data led to estimates of 56% with NIS-Flu and 58% with the NHIS no high-risk cohort. MarketScan estimates treating deaths with unknown vaccination status as unvaccinated were similar to NHIS estimates assuming 20% over-estimation of coverage by parental report. VE estimates among children with high-risk conditions were lower than among those without high-risk conditions for MarketScan as well as NHIS cohorts. Estimated VE among children with high-risk conditions remained statistically significant after decreasing NHIS coverage estimates by 10% while that among children without high-risk conditions remained significant when NHIS estimates were decreased by 20%.

DISCUSSION

We utilized national surveillance data on laboratory-confirmed influenza deaths and three comparison cohorts over four influenza seasons to estimate the effectiveness of influenza vaccination to prevent influenza-associated pediatric deaths. Best estimates using NHIS survey data suggested that vaccination reduced the risk of influenza-associated death by half among children with high-risk conditions and by nearly two-thirds among children without high-risk conditions. Despite high prevalence (53%) of underlying conditions that increase risk of severe influenza-related complications, only one in four children who died with laboratory-confirmed influenza had been vaccinated. These results reinforce the need to increase influenza vaccination coverage, especially among children at increased risk of influenza-related complications and death.

To our knowledge, this is the first study to use laboratory-confirmed outcomes to investigate influenza vaccine effectiveness against influenza-associated deaths. Observational studies that have used nonspecific outcomes, such as all-cause mortality, have frequently over-estimated effects of influenza vaccination on mortality in the elderly.[20–22] Estimates of VE against death from this analysis were similar to VE against medically attended influenza among pediatric patients for the same seasons. For 2011-2012 through 2013-2014, estimated VE against medically attended influenza ranged from 45% to 57% among young children (ages 6 months through 8 years), and from 39% to 58% among older children aged 9 to 17 years.[23–26] In addition, estimated VE against severe life-threatening influenza among children admitted to pediatric intensive care units during the 2010-2011 and 2011-2012 seasons was 74%.[27] VE against medically attended influenza has been used in models to estimate deaths averted by influenza vaccination.[28] Results of this analysis support the use of VE against medically attended influenza to estimate deaths averted by influenza vaccination.

Case-cohort analyses have previously been used to estimate influenza VE against laboratory-confirmed influenza,[29] effectiveness of seasonal influenza vaccine against influenza

A(H1N1)pdm09-associated illness,[30] and risk factors for hospitalization and death due to influenza A(H1N1)pdm09 infection.[31] In the main analyses, VE estimates were based on comparisons to NHIS and NIS-Flu, the two surveys used to measure influenza vaccine coverage among U.S. children. NHIS includes coverage estimates among children with high-risk conditions and NIS-Flu, with its larger sample size, provides state-level vaccination coverage. NHIS has been considered the most representative source for influenza vaccination coverage estimates among children[15] and is used as the data source to track progress towards Healthy People 2020 goals.[32] VE estimates based on NIS-Flu were similar to those based on the NHIS cohort without high-risk conditions.

This study highlights the importance of annual influenza vaccination for children, especially those with underlying high-risk medical conditions. Previous reports have highlighted the high prevalence of underlying high-risk conditions among children who die from influenza-related complications, including neurologic disorders and conditions associated with underlying chromosomal abnormalities and genetic syndromes.[3, 7, 33] While children with high-risk conditions in both the NHIS and MarketScan data were more likely than children without high-risk conditions to be vaccinated, vaccination coverage among high-risk children remained below the Healthy People 2020 target of 70% during these seasons.[32] Because of increased risk of severe complications and influenza-associated death among children with underlying conditions, vaccination is especially important for these children. Previous reports have also highlighted the occurrence of influenza-associated death in previously healthy children with no reported high risk conditions.[3, 34] The present study indicates that while VE estimates tended to be higher among children without underlying high risk conditions, significant protection was demonstrated for both groups of children for most seasons.

This analysis is subject to several limitations. Coverage estimates from NIS-Flu and NHIS rely on accuracy of parental report of influenza vaccination, which has been found to over-estimate provider report of coverage.[18] Over-reporting may be more common for adolescents and children with high-risk conditions.[19] The MarketScan database only included privately insured children and vaccination rates based on insurance claims of influenza vaccination were lower than those based on reported vaccination for the NHIS cohort. However, MarketScan estimates were also lower than observed vaccination rates (53% to 56% among children aged 6 months through 8 years and 37% to 43% among those aged 9-17 years) among influenza-negative children enrolled in the outpatient Influenza Vaccine Effectiveness network from 2011-2012 to 2013-2014.[23–25] Sensitivity analysis suggested that vaccination still provided protection against death assuming 10% to 20% over-reporting in NHIS, which resulted in similar estimates to comparisons with MarketScan cohorts. An alternative source of comparison coverage would be immunization information systems, but reporting of influenza vaccination for children is not mandatory in all states.[35] The majority of pediatric deaths with unknown vaccination status had no documentation of influenza vaccination in immunization information systems and were likely unvaccinated; sensitivity analyses treating these deaths as unvaccinated resulted in higher VE estimates. Vaccination coverage in the comparison cohorts was likely intermediate between estimates based on parental report and those based on insurance claims.[18] Finally, our analysis excluded deaths among infants who became eligible for vaccination after November 1 of

each season and included partially vaccinated children; partial vaccination provided no protection against severe influenza in a study conducted among children with influenza admitted to pediatric intensive care units.[27]

Results of this study suggest that vaccination reduced the risk of influenza-associated death among children and adolescents and add to the evidence of benefits of influenza vaccination for children. Annual vaccination is an important strategy to prevent influenza and influenza-associated complications and deaths. These results support current recommendations for annual influenza vaccination for all children ≥6 months of age.

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Abbreviations

ACIP	Advisory Committee on Immunization Practices
CI	credible interval
OR	odds ratio
VE	vaccine effectiveness

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Table of Contents Summary

This study estimates influenza vaccine effectiveness against deaths among children with and without underlying high-risk medical conditions using a case-cohort approach.

What's Known on This Subject

Annual influenza vaccination is recommended beginning at 6 months of age to prevent influenza and its complications. Most influenza-associated pediatric deaths occur in unvaccinated children. Evidence for effectiveness of vaccination in preventing influenza-associated deaths is needed.

What This Study Adds

This study estimated influenza vaccine effectiveness of 65% (95% confidence interval: 54-73) to prevent laboratory-confirmed influenza-associated death among children. Vaccine effectiveness was lower for children with underlying medical conditions but protection remained significant. Sensitivity analyses support the robustness of these findings.

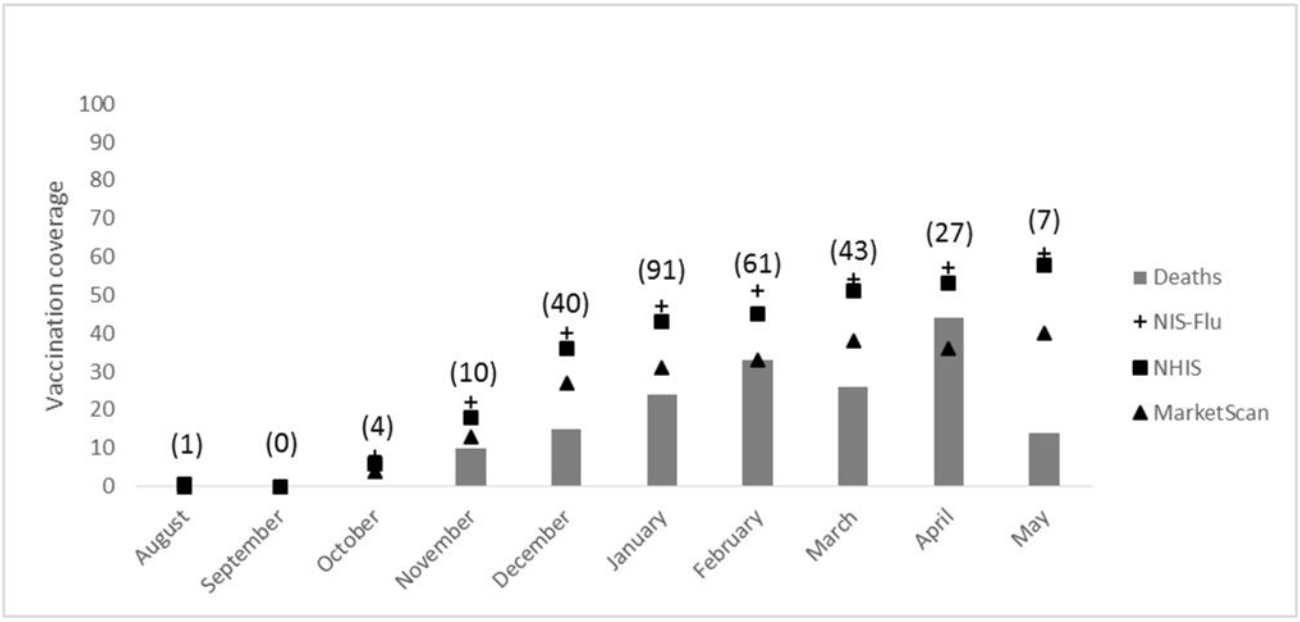

Figure. Comparison of Vaccination Coverage Among Influenza-Associated Pediatric Deaths and Comparison Cohorts During Four Influenza Seasons, According to Month of Death

Note: Number of deaths shown in parentheses. Coverage estimates for comparison cohorts correspond to month preceding case illness onset.

Table 1

Characteristics of Influenza-Associated Pediatric Deaths With Known Vaccination Status, United States, 2010-11 to 2013-14 Influenza Seasons (N=291)[a]

	Total		Vaccinated[b]	
Characteristic	**No.**	**%**	**No.**	**% vaccinated**
Overall	291		75	26
Gender				
Female	135	46	30	22
Male	156	54	45	29
Age				
6 months to 4 years	93	32	31	33
5 to 12 years	128	44	26	20
13 to 17 years	70	24	18	26
Race/ethnicity				
White, non-Hispanic	154	53	42	27
Hispanic or Latino	57	20	12	21
Black, non-Hispanic	39	13	3	8
Asian/Pacific Islander	12	4	8	67
American Indian/Alaskan Native	7	2	2	29
Identified by ≥2 races	1	<1	1	100
Unknown	21	7	7	33
High-risk medical conditions [c]				
No high-risk medical conditions	135	47	27	20
One or more high-risk medical condition[d]	153	53	47	31
Chronic pulmonary disease (including asthma)	72	25	25	35
Metabolic disorders (including diabetes)	18	6	8	44
Neurologic and neuromuscular disorders	75	26	25	33
Renal disease	3	1	0	0
Cardiac or congenital heart disease	30	10	7	23
Immunosuppressive condition	15	5	7	47
Pregnancy	2	1	0	0
Two or more high-risk medical conditions[d]	46	16	17	37
Other high-risk conditions [e]	37	13	13	35
Location of death [f]				
In hospital	189	66	54	29
Emergency department	54	19	17	31
Outside hospital	45	15	3	7
Influenza virus type/subtype				
Influenza A	173	59	44	25
A(H1N1)pdm09	87	30	24	28
A(H3N2)	68	23	15	22

Characteristic	Total		Vaccinated[b]	
	No.	%	No.	% vaccinated
A, subtype not distinguished				
Influenza B	113	39	31	27
Co-infection (types A and B)	5	2	0	0

[a] Excludes children with unknown vaccination status.

[b] Receipt of at least one dose of influenza vaccine ≥14 days before onset of illness for season in which death occurred.

[c] Case investigation form indicates presence of high-risk condition, as defined by Advisory Committee on Immunization Practices guidance for conditions that increase risk for complications of influenza. High risk status was not reported for 3 deaths.

[d] More than one medical condition could be reported for each pediatric death.

[e] Includes chromosomal abnormalities, genetic syndromes and mitochondrial disorders.

[f] Location of death was missing for 3 deaths.

Table 2

Percentage Vaccinated Among Influenza-Associated Pediatric Deaths Compared to National Immunization Survey-Flu Cohorts, With Vaccine Effectiveness Estimates by Season and Age Group

Stratum	Influenza-Associated Deaths[a]		National Immunization Survey-Flu[b]		Vaccine Effectiveness[c]	
	No. vaccinated/Total	% vaccinated	Average % vaccinated (LCL, UCL)		%	95% CI
Overall						
	75/291	26	48	(42, 55)	65	(54, 74)
Age						
6 months - 4 years	31/93	33	55	(47, 62)	61	(40, 76)
5 - 12 years	26/128	20	50	(44, 56)	76	(63, 85)
13 -17 years	18/70	26	36	(30, 43)	40	(0, 67)
Season						
2010-11	22/73	30	47	(39, 55)	54	(22, 74)
2011-12	4/21	19	51	(44, 59)	80	(41, 95)
2012-13	28/116	24	46	(39, 52)	64	(46, 77)
2013-14	21/81	26	53	(47, 58)	71	(52, 83)
Influenza virus						
Influenza A	44/173	25	48	(41 55)	66	(53, 76)
Influenza B	31/113	27	49	(42, 55)	62	(42, 75)

LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval.

[a] Excludes cases with unknown vaccination status.

[b] Average influenza vaccine coverage estimates (with lower and upper 95% confidence limits) for National Immunization Survey-Flu comparison cohorts, paired by season, age category and state of residence with pediatric deaths, during month ending >14 days prior to case illness onset.

[c] VE calculated as 100 × (1 - Odds Ratio [OR]) from logistic regression comparing odds of vaccination among influenza-associated deaths to odds of vaccination in NIS-Flu comparison cohorts, with Bayesian 95% credible intervals.

Table 3

Percentage Vaccinated Among Influenza-Associated Pediatric Deaths Compared to National Health Interview Sample According to High-Risk Status, with Vaccine Effectiveness Estimates by Season and Age Group

Stratum	Children with High-Risk Medical Conditions						Children without High-Risk Medical Conditions					
	Influenza-Associated Deaths[a]		National Health Interview Survey Sample[b]		Vaccine Effectiveness[c]		Influenza-Associated Deaths[a]		National Health Interview Survey Sample[b]		Vaccine Effectiveness[c]	
	No. vaccinated/Total	% vaccinated	Average % vaccinated (LCL, UCL)		%	95% CI	No. vaccinated/Total	% vaccinated	Average % vaccinated (LCL, UCL)		%	95% CI
Overall	47/153	31	47	(37, 57)	51	(31, 67)	27/135	20	40	(38, 43)	65	(47, 78)
Age												
6 months – 4 years	14/38	37	48	(37, 60)	39	(−22, 71)	16/54	30	46	(43, 49)	52	(14, 74)
5 – 12 years	19/72	26	49	(41, 57)	65	(41, 81)	7/55	13	39	(37, 42)	79	(57, 92)
13 – 17 years	14/43	33	41	(31, 51)	33	(−28, 67)	4/26	15	30	(27, 33)	60	(−5, 89)
Season												
2010-11	12/29	41	45	(36, 54)	13	(−85, 62)	9/43	21	40	(37, 42)	63	(24, 84)
2011-12	3/13	23	48	(39, 56)	73	(0, 94)	1/8	13	45	(42, 47)	89	(16, 99)
2012-13	21/64	33	43	(34, 53)	38	(0, 65)	7/52	14	37	(34, 39)	76	(46, 90)
2013-14	11/47	23	53	(42, 63)	75	(50, 88)	10/32	31	46	(43, 49)	48	(−11, 77)
Influenza Virus												
Influenza A	26/95	27	46	(36, 56)	59	(35, 74)	18/78	23	41	(39, 44)	59	(31, 77)
Influenza B	21/55	38	48	(39, 57)	35	(−13, 63)	9/55	16	38	(36, 41)	71	(43, 87)

LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval.

[a] Excludes cases with unknown vaccination status.

[b] Average influenza vaccine coverage estimates (with lower and upper 95% confidence limits) for National Health Interview Survey comparison cohorts, paired by season, age category and high risk status with pediatric deaths, during month ending >14 days prior to case illness onset.

[c] Vaccine effectiveness estimates and Bayesian 95% credible interval estimated from logistic regression.

Table 4

Prevalence of High Risk Conditions and Influenza Vaccination Among Children With Influenza-Associated Death and Children in Marketscan Commercial Claims Database, 2010-2014

High-risk category[a]	Influenza-associated pediatric deaths (N=291)			MarketScan Commercial Claims dataset (N=6,543,363)[b]		
	No.	% total	No. (%) vaccinated	No.	% total	No. (%) vaccinated[c]
No high-risk condition	138	47	28 (20)	5 815 031	89	1 557 855 (27)
Pulmonary conditions, including asthma	39	13	11 (28)	414 868	6	175 528 (42)
Metabolic disorders	6	2	2 (33)	33 248	<1	11 250 (34)
Neurologic disorders	37	13	11 (30)	70 631	1	24 627 (35)
Cardiac and congenital heart diseases	17	6	4 (24)	45 448	<1	16 367 (36)
Immunosuppressive conditions	6	2	2 (33)	58 094	1	18 022 (31)
Pregnancy[d]	2	1	0 (0)	18 523	<1	6 316 (34)
2 or more high-risk conditions	46[e]	16	17 (37)	83 146	1	37 114 (45)

[a] Influenza associated pediatric deaths and children from MarketScan database were classified into mutually exclusive high-risk categories based on groups at increased risk of complications, hospitalizations or death due to influenza according to the Advisory Committee for Immunization Practices; children with two or more high-risk conditions included those with conditions from two or more ACIP high-risk categories.

[b] Numbers and percentages for MarketScan Commercial Claims dataset are averages over four influenza seasons, 2010-2011 through 2013-2014.

[c] Average over four influenza seasons of the number vaccinated by May of each season

[d] Pregnancy restricted to children aged 13 to 17 years.

[e] Among influenza-associated pediatric deaths, includes children with pulmonary conditions (n=33), metabolic disorders (n=12), neurologic disorders (n=38), cardiac diseases (n=13) and immunosuppressive conditions (n=9).

Table 5

Sensitivity Analysis for Vaccine Effectiveness Estimates With Adjustments to Case and Comparison Cohort Vaccination Status

Sensitivity analysis	No. flu-related deaths	% cases vaccinated	Average % vaccinated (LCL, UCL)	VE	95% CI
NIS-Flu comparison cohort			**NIS-Flu cohort**[a]		
Excluding deaths with unknown vaccination status	291	26	48 (42, 55)	65	(54, 74)
Treating deaths with unknown vaccination status as unvaccinated	358	21	49 (42, 55)	74	(66, 80)
Assuming 10% under-estimation[b]	291	26	53 (46, 59)	72	(64, 79)
Assuming 10% over-estimation[b]	291	26	44 (38, 49)	56	(44, 67)
Assuming 20% over-estimation[b]	291	26	39 (34, 44)	46	(29, 59)
NHIS high-risk cohort			**NHIS high-risk cohort**[c]		
Excluding deaths with unknown vaccination status	153	31	47 (37, 57)	51	(31, 67)
Treating deaths with unknown vaccination status as unvaccinated	182	26	47 (37, 56)	62	(47, 73)
Assuming 10% under-estimation[b]	153	31	52 (41, 62)	61	(44, 73)
Assuming 10% over-estimation[b]	153	31	42 (34, 51)	41	(16, 59)
Assuming 20% over-estimation[b]	153	31	37 (30, 45)	27	(-4, 50)
NHIS no high-risk cohort			**NHIS no high-risk cohort**[c]		
Excluding deaths with unknown vaccination status	135	20	40 (38, 43)	65	(47, 78)
Treating deaths with unknown vaccination status as unvaccinated	167	16	40 (38, 43)	73	(60, 83)
Assuming 10% under-estimation[b]	135	20	44 (41,47)	71	(56, 81)
Assuming 10% over-estimation[b]	135	20	36 (34, 39)	58	(35, 73)
Assuming 20% over-estimation[b]	135	20	32 (30, 34)	49	(24, 68)
MarketScan high-risk cohort			**MarketScan high-risk cohort**[c]		
Excluding deaths with unknown vaccination status	153	31	35	18	(-17, 42)[d]
Treating deaths with unknown vaccination status as unvaccinated	182	26	35	38	(12, 56)[d]
MarketScan no high-risk cohort			**MarketScan no high-risk cohort**[e]		
Excluding deaths with unknown vaccination status	135	20	28	38	(4, 60)[d]
Treating deaths with unknown vaccination status as unvaccinated	167	16	27	50	(24, 67)[d]

NIS-Flu, National Immunization Survey-Flu; NHIS, National Health Interview Survey; LCL, lower 95% confidence limit; UCL, upper 95% confidence limit; CI, credible interval; VE, vaccine effectiveness.

[a] Average coverage estimate for NIS-Flu cohort paired with pediatric death by season, age group, state of residence and month preceding illness onset.

[b] Survey coverage estimates for each comparison cohort were increased by 10% or reduced by 10% or 20%

[c] Average national coverage estimate for NHIS and MarketScan comparison cohorts paired with pediatric death by season, age group, high risk status, and month preceding illness onset.

[d] 95% confidence intervals for VE from logistic regression with odds of vaccination in MarketScan comparison cohort entered as an offset.

[e] For children without high risk conditions, state-specific coverage estimates were used for MarketScan comparison cohorts paired with pediatric death by season, age group and month preceding illness onset.